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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	John T. Mulligan and John C. Tabone
Application No.	:	09/872,761
Filed	:	June 1, 2001
For	:	METHODS FOR IMPROVING THE SEQUENCE FIDELITY OF SYNTHETIC DOUBLE-STRANDED OLIGONUCLEOTIDES
Art Unit	:	1623
Docket No.	:	340078.401
Date	:	September 25, 2001

Box Missing Parts
Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT REGARDING SEQUENCE DISCLOSURES

Commissioner for Patents:

In response to the Notice to File Missing Parts dated August 8, 2001, please amend the above-identified application as follows:

In the Specification:

Please insert the enclosed "Sequence Listing" immediately after the section of the specification entitled "Abstract of the Disclosure" on page 25.

Please replace the paragraph beginning at page 11, line 17, with the following rewritten paragraph:

A 205 base pair segment of the lacI gene with the sequence (SEQ ID NO:1):

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1     AATTCATAAA GGAGATATCA TATGAAACCG GTAACGTTAT ACGACGTCGC TGAATACGCC
61    GGCGTTTCTT ACCAGACCGT TTCTAGAGTG GTTAACCAGG CTTCACATGT TAGCGCTAAA
121   ACCCGGGAAA AAGTTGAAGC TGCCATGGCT GAGCTCAACT ACATCCCGAA CCGTGTTGCG
181   CAGCAGCTGG CTGGTAAACA AAGCT
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is synthesized using a set of overlapping double-stranded oligonucleotides.

Please replace the paragraph beginning at page 14, line 12, with the following rewritten paragraph:

One common side reaction of oligonucleotide synthesis is the formation of diaminopurine from a dG residue in the DNA chain. Modified oligonucleotides containing 2,6-diaminopurine are obtained from Trilink Biotechnologies (San Diego, CA) and incorporated into the 205 bp lacI gene fragment. Four samples were prepared as described in Example 1, with one diaminopurine residue (labeled **D** below) substituted for a dG residue in each sample.

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Oligonucleotide	Fragment Name	Base Replaced	SEQ ID NO:
5′ ACCGTTTCTA**D**AGTGGTTAACCAGG 3′	D-T86	86	2
5′ ACCGTTTCTAGA**D**TGGTTAACCAGG 3′	D-T88	88	3
5′ GGAAAAA**D**TTGAAGCTGCCATGGCT 3′	D-T133	133	4
5′ TT**D**CGCAGCAGCTGGCTGGTAAACAA 3′	D-T178	178	5

Please replace the paragraph beginning at page 15, line 3, with the following rewritten paragraph:

A second common side reaction of oligonucleotide synthesis is deamination of the N4-amine of deoxycytidine to form a uracil (dU) in the DNA chain. Modified oligonucleotides

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containing uracil (dU) are obtained from Midland Certified Reagent Company (Midland, TX) and incorporated into the 205 bp lacI gene fragment. Two samples were prepared as described in Example 1, with one uracil residue (labeled **dU** below) substituted for a dC residue in each sample.

Oligonucleotide	Fragment Name	Base Replaced	SEQ ID NO:
5′ TGAAGCCTGGTTAACCACT**dU**TAGAA 3′	U-B86	86	6
5′ AGCTCAGCCATGGCAGCTTCAA**dU**TT 3′	U-B133	133	7

Please replace the paragraph beginning at page 15, line 13, with the following rewritten paragraph:

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A third common side reaction of oligonucleotide synthesis is the formation of abasic sites by depurination of protected adenosine residues during chain elongation. Modified oligonucleotides containing uracil are obtained from Midland Certified Reagent Company (Midland, TX) and incorporated into the 205 bp lacI gene fragment. Two samples were prepared as described in Example 1, with one uracil residue (labeled **dU** below) substituted for a dA residue in each sample.

Oligonucleotide	Fragment Name	Base Replaced	SEQ ID NO:
5' AGCTCAGCCATGGCAGCTTCA**dU**CTT 3'	A-B134	134	8
5' TTGCGC**dU**GCAGCTGGCTGGTAAACAA 3'	A-T182	182	9

Please replace the paragraph beginning at page 16, line 7, with the following rewritten paragraph:

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The thermal and gradient conditions for isolating chemically-pure enriched sequence are calculated using the DHPLC Melt Program (http://insertion.stanford.edu/melt.html) available from Stanford University (Palo Alto, CA) and available for license from the Stanford University Office of Technology Licensing referring to the docket number S95-024. The 4 base single-stranded region on either end of the 205 base pair fragment is removed to give the following 197 base pair sequence (SEQ ID NO: 10).

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CATAAAGGAGATATCATATGAAACCGGTAACGTTATACGACGTCGCTGAA

TACGCCGGCGTTTCTTACCAGACCGTTTCTAGAGTGGTTAACCAGGCTTC

ACATGTTAGCGCTAAAACCCGGGAAAAAGTTGAAGCTGCCATGGCTGAGC

TCAACTACATCCCGAACCGTGTTGCGCAGCAGCTGGCTGGTAAACAA

Please replace the paragraph beginning at page 20, line 14, with the following rewritten paragraph:

The control and the four sequences containing the synthesis byproducts are listed below:

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5'- ATTCGCCCTTTGCCACTAAGCACCAGCGAAACGGTACTTACCGACACG-3' Control (SEQ ID NO:11)

5'-ATTCGCCCTTTGCCACTAAGCACCAGCGAAACGGTACT__ACCGACACG-3' n-1 (SEQ ID NO:12)

5'-ATTCGCCCTTTGCCACTAAGCACCAGCGAAACGGTACTT***T***ACCGACACG-3' n+ (SEQ ID NO:13)

5'-ATTCGCCCTTTGCCACTAAGCACCAGCGAAACGGTACTT***G***CCGACACG-3' T/G Mismatch (SEQ ID NO:14)

5'-ATTCGCCCTTTGCCACTAAGCACCAGCGAAACGGTACTTA***G***CGACACG-3' G/G Mismatch (SEQ ID NO:15)

REMARKS

The enclosed electronic and paper copies of the Sequence Listing include no new matter that goes beyond the original application as filed, but are supplied to fulfill the requirements as outlined in the Notice to File Missing Parts. Furthermore, the above amendments, which merely direct the insertion of the Sequence Listing and insertion of sequence identifiers, include no matter that goes beyond the original application as filed. Applicants respectfully submit that the above-identified application is now in compliance with 37 C.F.R. §§ 1.821-1.825.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The first of the attached pages is captioned "Version with Markings to Show Changes Made."

Respectfully submitted,
Seed Intellectual Property Law Group PLLC

Richard G. Sharkey, Ph.D.
Registration No. 32,629

RGS:mls

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031